Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use

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Abstract: BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is an important modulator of cognitive and social functioning in cocaine addiction but it is unclear whether ADHD symptoms and cocaine use display mutually aggravating interaction effects on cognition, social functioning, and depressive symptoms. Therefore, we investigated the interaction of cocaine use and adult ADHD on social and non-social cognition and depressive symptoms. METHODS: Twenty-four cocaine users with (CU+ADHD) and 30 without ADHD (CU-ADHD), 29 cocaine-naïve ADHD patients, and 40 cocaine-naïve healthy controls underwent comprehensive neuropsychological testing including assessment of social cognition (cognitive/emotional empathy and Theory-of-Mind). Additionally, depressive symptoms were measured with the Beck Depression Inventory. RESULTS: The effect size of global cognitive impairment was largest in CU+ADHD (d=1.22 vs. controls) followed by CU-ADHD (d=0.74), and cocaine-naïve ADHD patients (d=0.33). A similar pattern appeared regarding depressive symptoms (CU+ADHD: d=1.47; CU-ADHD: d=0.49, ADHD: d=0.34). In the measures of Theory-of-Mind (CU+ADHD: d=0.76; CU-ADHD: d=0.06, ADHD: d=0.01) and cognitive empathy (CU+ADHD: d=0.80; CU-ADHD: d=0.39, ADHD: d=-0.11) only CU+ADHD showed moderate to large impairments. Moreover, two-way analyses of covariance revealed a significant interaction effect of the factors ADHD and cocaine use on depressive symptoms ($p<0.05$) and Theory-of-Mind ($p<0.05$) but not on global cognitive performance ($p=0.64$). CONCLUSIONS: When occurring together, cognitive impairments associated with both ADHD and cocaine use are largely additive, whereas both factors seem to mutually potentiate one another with respect to mood and mental perspective-taking disturbances. Given the high comorbidity between ADHD and cocaine use, longitudinal studies are needed to investigate the origin of these potentiated impairments.

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder (ADHD) is an important modulator of cognitive and social functioning in cocaine addiction but it is unclear whether ADHD symptoms and cocaine use display mutually aggravating interaction effects on cognition, social functioning and depressive symptoms. Therefore, we investigated the interaction of cocaine use and adult ADHD on social and non-social cognition and depressive symptoms.

Methods: Twenty-four cocaine users with (CU+ADHD) and 30 without ADHD (CU-ADHD), 29 cocaine-naïve ADHD patients, and 40 cocaine-naïve healthy controls underwent comprehensive neuropsychological testing including assessment of social cognition (cognitive/emotional empathy and Theory-of-Mind). Additionally, depressive symptoms were measured with the Beck Depression Inventory.

Results: The effect size of global cognitive impairment was largest in CU+ADHD (d=1.22 vs. controls) followed by CU-ADHD (d=0.74), and cocaine-naïve ADHD patients (d=0.33). A similar pattern appeared regarding depressive symptoms (CU+ADHD: d=1.47; CU-ADHD: d=0.49, ADHD: d=0.34). In the measures of Theory-of-Mind (CU+ADHD: d=0.76; CU-ADHD: d=0.06, ADHD: d=0.01) and cognitive empathy (CU+ADHD: d=0.80; CU-ADHD: d=0.39, ADHD: d=-0.11) only CU+ADHD showed moderate to large impairments. Moreover, two-way analyses of covariance revealed a significant interaction effect of the factors ADHD and cocaine use on depressive symptoms (p<.05) and Theory-of-Mind (p<.05) but not on global cognitive performance (p=.64).

Conclusions: When occurring together, cognitive impairments associated with both ADHD and cocaine use are largely additive, whereas both factors seem to mutually potentiate one another with respect to mood and mental perspective-taking disturbances. Given the high comorbidity between ADHD and cocaine use, longitudinal studies are needed to investigate the origin of these potentiated impairments.

Keywords: stimulants, depression, affective disorder, mentalizing, emotion recognition, chronic use

1. INTRODUCTION

With an estimated 17 million past-year users cocaine remains one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2015). Because of its negative health consequences and addictive potential, cocaine use represents a major issue in public health (Nutt et al., 2007). Attention-deficit/hyperactivity disorder (ADHD) is another major public health issue (Ballon et al., 2015), with an estimated worldwide prevalence of about 5% in children (Polanczyk et al., 2014) and symptoms that persist into adulthood in up to 65% of patients (Faraone et al., 2006). At more than 20%, the prevalence of adult ADHD appears to be much higher in individuals with cocaine use disorder compared with the general population (Perez de Los Cobos et al., 2011; van Emmerik-van Oortmerssen et al., 2012; Vonmoos et al., 2013a). Furthermore, in a sample of adult patients seeking treatment for cocaine addiction, 35% were found to have ADHD (Lambert and Hartsough, 1998). These numbers are in line with the assumption that adolescents with ADHD are about twice as likely as healthy individuals to develop a substance use disorder (Biederman et al., 1995).

Recent findings from the Zurich Cocaine Cognition Study (ZuCo^{2}St) confirmed that recreational and dependent cocaine users displayed considerable impairments in attention, working memory, declarative memory, and executive functions that were aggravated with increased use (Vonmoos et al., 2013a). Furthermore, recreational and dependent cocaine users showed less emotional empathy, and specifically dependent users displayed difficulties in mental and emotional perspective-taking (also called "mentalizing" or "Theory-of-Mind"), higher delay aversion, and decreased planning abilities (Hulka et al., 2014; Preller et al., 2014). In the ZuCo^{2}St, social and non-social cognition were strongly moderated by comorbid ADHD symptoms, since the combination of cocaine use and ADHD symptoms was associated with much more pronounced deficits (Preller et al., 2014; Vonmoos et al., 2013a).

Cocaine use appears to impact neurotransmitter systems in brain regions thought to be altered in ADHD patients: Chronic cocaine use has been linked to alterations in the fronto-striatal dopamine system (Beveridge et al., 2008; Garavan and Hester, 2007; Volkow et al., 2009a; Volkow et al., 2004) and noradrenergic changes in the thalamus and locus coeruleus (Ding et al., 2010). Moreover, structural and functional changes in several areas of the prefrontal cortex have been linked to cognitive

deficits in dependent cocaine users (Beveridge et al., 2008; Garavan and Hester, 2007; Goldstein et al., 2004). Remarkably, fronto-striatal dysfunctions and changes in catecholaminergic neurotransmitter systems appear to also play a crucial role in the etiology of ADHD (Brennan and Arnsten, 2008; Del Campo et al., 2011; Tripp and Wickens, 2009). In particular, disturbances in cognitive functions such as vigilance, working memory, planning, and response inhibition—as well as problems in motivational processes, such as delay aversion—are associated with both ADHD (Nigg, 2005; Willcutt et al., 2005) and cocaine use (Hulka et al., 2014; Vonmoos et al., 2013a; Vonmoos et al., 2013b). In both cases, these effects have been proposed to depend on changes in the dopamine and noradrenaline system (Gould et al., 2014; Sofuoglu, 2010; Tripp and Wickens, 2009). Recently, also problems in more complex cognitive functions such as social cognition and interaction have been demonstrated in recreational and dependent cocaine users as well as in patients with ADHD (Bora and Pantelis, 2016; Hulka et al., 2014; 2013; Preller et al., 2014). Additionally, both, patients with cocaine addiction and with ADHD have an increased risk for developing depressive symptoms (Connor et al., 2003; Rounsaville, 2004; Swendsen and Merikangas, 2000).

To our knowledge, the interaction of ADHD symptoms and cocaine use with regard to cognitive and socio-cognitive functions as well as to depressive symptoms has not been investigated in detail yet. Thus, it remains unclear whether the pronounced cognitive and socio-cognitive impairments of cocaine users with ADHD symptoms arise from a combination of ADHD and cocaine use or can be explained by ADHD alone (Preller et al., 2014; Vonmoos et al., 2013a). Therefore, we recruited a group of ADHD patients without illegal drug use and compared them with cocaine users with and without ADHD and to stimulant-naïve healthy controls so as to investigate the presumed interactions between ADHD and cocaine use. We hypothesized that ADHD and cocaine use would reveal cumulative or even multiplicative effects.

2. METHODS

2.1 Participants

We recruited 29 ADHD patients who reported no illegal drug use, 24 cocaine users with ADHD (CU+ADHD), 30 cocaine users without ADHD (CU-ADHD), and 40 stimulant-naïve healthy controls and matched the groups for age and sex (see Supplementary Methods S1 for recruitment details). All participants had to be between 18 and 60 years old and fluent in German. Exclusion criteria for all participants were current or previous neurological disorders or head injury, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, and the use of prescription drugs affecting the central nervous system (except for methylphenidate and dexamphetamine for the ADHD group) as well as a lifetime history of opioid use. For controls and ADHD patients, further exclusion criteria were any Axis-I *DSM-IV* psychiatric disorder (with the exception of ADHD), any form of addiction (except nicotine), and regular illegal drug use (lifetime use >15 occasions, except cannabis). Specific exclusion criteria for the cocaine user groups were polytoxic drug use, any Axis-I *DSM-IV* adult psychiatric disorder (other than ADHD in CU+ADHD) with exception of cocaine, nicotine, and alcohol abuse/dependence and history of depression (acute major depression was excluded). Inclusion criteria for the cocaine user groups were cocaine use of at least 0.5g/month, cocaine as the preferred illegal drug, and a current abstinence period of less than 6 months. All participants were asked to abstain from illegal substances for at least three days and from alcohol for at least 24h prior to testing. Compliance was controlled by urine toxicology, and self-reported drug use was controlled by a 6-month hair testing (see Supplementary Methods S2). Of the 29 cocaine-naïve ADHD patients, 24 received stimulant treatment prior to the study (23 participants received methylphenidate, 1 participant received dexamphetamine) while four patients showed no history of stimulant medication. ADHD patients were asked not to use prescription stimulants or any other medication for 24h prior to testing. The study was approved by the Cantonal Ethics Committee of Zurich, and all participants gave written informed consent and were compensated for their participation.

2.2 Clinical Assessment

Trained psychologists conducted the Structured Clinical Interview for Axis-I *DSM-IV* disorders in order to exclude participants with an Axis-I *DSM-IV* psychiatric disorder. Drug use was assessed with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). ADHD diagnoses and current severity of ADHD symptoms were evaluated with the ADHD self-rating scale (ADHD-SR) (Rosler et al., 2004) corresponding to *DSM-IV* criteria. Furthermore, the German short version of the Wender Utah Rating Scale (WURS-k) measuring ADHD symptoms present in childhood was used in the ADHD sample (Retz-Junginger et al., 2002). Depressive symptoms – as an outcome measure - were assessed with the Beck Depression Inventory (BDI) (Beck et al., 1961). Premorbid verbal intelligence was estimated with a German vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest) (Lehrl et al., 1995). Severity of tobacco dependence was measured by the Fagerström Test of Nicotine Dependence (Heatherton et al., 1991). Finally, to measure present cocaine craving in cocaine users, the brief version of the cocaine craving questionnaire (CCQ) was applied (Sussner et al., 2006).

2.3 Neuropsychological Assessment

Cognitive performance was assessed with four tests from the Cambridge Neuropsychological Test Automated Battery (Strauss et al., 2006): Rapid Visual Information Processing, Spatial Working Memory, Intra/Extra-Dimensional Set Shifting, and Paired Associates Learning. Additionally, a German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001) and the Letter Number Sequencing Test were administered (Wechsler, 1997). As previously published (Vonmoos et al., 2013a; Vonmoos et al., 2014), 15 predefined test parameters underwent z-transformation on the basis of means and standard deviations of the control group and were combined into four cognitive domains (Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Vonmoos et al., 2013a; Woicik et al., 2009): attention, working memory, declarative memory, and executive functions (see Supplementary Methods S3 for details). These four domains were equally integrated into a global cognitive index (GCI). To avoid the accumulation of alpha-errors, we focused our analysis on these four domains and the GCI. However, we reported single neuropsychological test scores in the Supplementary Material (Supplementary Table S1). Two aspects of social cognition—Theory-of-Mind

and empathy—were assessed with the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006) and the Multifaceted Empathy Test (MET) (Dziobek et al., 2008), both of which have been described in detail in our previous work (see also Supplementary Methods S4) (Preller et al., 2014).

2.4 Statistical Analysis

We performed the statistical analyses with SPSS 22.0 for Windows. Demographic and drug use data for all groups were analyzed with Pearson's chi-square test and analyses of variance (ANOVA) followed by Sidak-corrected post-hoc comparisons where appropriate. To investigate group differences over all groups in cognitive and emotional parameters, we performed analysis of covariance (ANCOVA) or multivariate analysis of covariance (MANCOVA) followed by Sidak-corrected post-hoc comparisons. To investigate the interaction between cocaine use and ADHD, we analyzed the data with two-way ANCOVA using the fixed factors of "ADHD" and "cocaine use" (both yes/no). Following significant interaction effects, simple effects were calculated. The significance threshold was set at $p<.05$. To examine if cognitive performance and depressive symptoms were associated with craving for cocaine, Pearson's product moment correlations between relevant outcome measures and the CCQ sum score were calculated (Supplementary Table S2). In order to avoid alpha-error accumulation, the significance threshold was set to $p<.01$ for correlation analyses. Because age is a common confounding variable in investigations of cognition (and especially social cognition), it was introduced as a covariate (Horning et al., 2012; Verhaeghen and Salthouse, 1997). Because of significant group differences, years of education (YoE) was introduced as a further covariate. We have previously shown that the moderating effect of the co-factor ADHD on global cognitive performance in cocaine users was large with an effect size of Cohen's f=0.49 and a partial eta-square=0.195 (Vonmoos et al., 2013a). In an a priori power analysis, we therefore assumed a lower effect size of f=0.40, an α-error probability of 5%, and a conservative power of 90% for the present ANCOVA design with 4 groups and 2 covariates, suggesting a total minimum sample size of 93 individuals.

3. RESULTS

3.1 Demographic Characteristics and Drug Use

The groups did not differ significantly in age and sex distribution (Table 1). However, the groups significantly differed in YoE and verbal IQ: CU+ADHD had fewer YoE and lower verbal IQ scores than controls and ADHD patients. As expected, the four groups differed in ADHD symptom severity as measured by the ADHD-SR. The ADHD group reported the most severe ADHD symptom scores, which differed significantly from controls and CU-ADHD but importantly did not differ significantly from CU+ADHD (p=.49). On the WURS-k, the ADHD group reported a mean score of 36.8±15.9 (SD), which is above the diagnostic cut-off of 30 points (Retz-Junginger et al., 2002).

Notably, CU-ADHD did not differ significantly from CU+ADHD for any self-reported cocaine use parameter or for frequency of *DSM-IV* cocaine dependence (Table 1). Moreover, CU+ADHD and CU-ADHD showed no significant differences regarding cocaine hair concentrations or frequency of cocaine-positive urine testings. Accordingly, CU-ADHD and CU+ADHD did also not differ significantly in the CCQ sum score. In addition, correlation analysis showed that test performance and depressive symptom scores did not correlate with craving for cocaine (Supplementary Table S2). Hair testings confirmed a clear preference for cocaine versus other drugs for both groups (Supplementary Table S3) and revealed the highest methylphenidate concentrations in ADHD patients (Table 1). CU+ADHD and CU-ADHD smoked significantly more cigarettes than the ADHD patients, and CU+ADHD also smoked more frequently than controls. Both cocaine user groups reported greater weekly alcohol consumption than the ADHD group.

3.2 Cognition

One-way ANCOVAs (with YoE and age as covariates) performed for the GCI and the four cognitive domains revealed significant group differences in the GCI ($F(3,117)=12.12$, $p<.001$), working memory ($F(3,117)=8.87$, $p<.001$), declarative memory ($F(3,117)=14.07$, $p<.001$), executive functions ($F(3,117)=2.68$, $p<.05$), and the attention domain score ($F(3,117)=4.16$, $p<.01$). In addition, clear

linear trends (controls>ADHD>CU-ADHD>CU+ADHD) were found (p<.001–.01) in all cognitive domains (Fig. 1).

Sidak post-hoc comparisons revealed significant differences between controls and both cocaine-using groups in the GCI, working memory, and declarative memory (p<.001–.01), indicating cognitive impairments in both user groups. CU+ADHD also differed from controls in attention (p<.01) and performed worse than the ADHD group in the GCI and the two memory domains (p<.001–.01). CU-ADHD performed better than CU+ADHD for declarative memory (p<.05) (Fig. 1). ADHD patients showed no significant performance deficits compared with the controls in any of the four domains or the GCI.

A two-way ANCOVA revealed significant main effects of ADHD ($F(1,117)=7.62$, p<.01) and cocaine use ($F(1,117)=28.49$, p<.001) on the GCI but no significant interaction effect ($F(1,117)=.21$, p=.64)(Fig. 2a). Similar effects were found for the other domains—except for attention and executive functions, for which the main effects for ADHD were not significant ($F(1,117)=2.58$ and 0.61, p=.11 and .44, respectively).

3.3 Social cognition

The MANCOVA (with YoE and age as covariates) performed for the z-transformed variables cognitive empathy (CE), explicit emotional empathy (EEE), and implicit emotional empathy (IEE) on the MET showed a significant main effect for group using Hotelling's trace ($V=.21$, $F(9,341)=2.66$, p<.01). Groups differed significantly in CE ($F(3,117)=4.62$, p<.01). In addition, linear trends (controls>ADHD>CU-ADHD>CU+ADHD) were found (p<.001–.05) for all of the three MET variables. For Theory-of-Mind, an ANCOVA revealed significant group differences ($F(3,117)=3.68$, p<.05) in the MASC sum score (Supplementary Fig. S1) and a significant linear trend (p<.01, controls>ADHD>CU-ADHD>CU+ADHD). Sidak post-hoc comparisons revealed that CU+ADHD made more errors than controls and ADHD patients in CE and Theory-of-Mind (p<.01–.05) and that CU-ADHD performed better than CU+ADHD on the MASC (p<.05). Analysis of the different MASC

error types are shown in the Supplementary Material (Supplementary Fig. S2). Notably, ANCOVA for overmentalizing errors (excessive Theory-of-Mind) yielded a significant main effect for group ($F(3,117)=4.08$, $p<.01$), and Sidak post-hoc comparisons revealed significant differences between CU+ADHD and ADHD patients and between CU+ADHD and controls ($p<.01$ and $<.05$).

Two-way ANCOVAs on the MET scores revealed a significant main effect for cocaine use on CE ($F(1,117)=12.65$, $p<.001$) and IEE ($F(1,117)=7.70$, $p<.01$) but not on EEE ($F(1,117)=3.61$, $p=.06$). For ADHD, no significant main effects were found ($F(1,117)=0.02–0.85$, $p=.36–.88$), and the two factors showed no significant interaction effects ($F=(1,117)=0.18–2.16$, $p=.14–.67$).

The two-way ANCOVA on Theory-of-Mind revealed that the interaction of ADHD and cocaine use had a significant effect on mental and emotional perspective-taking performance ($F(1,117)=4.09$, $p<.05$). The main effects for ADHD ($F(1,117)=3.93$, $p<.05$) and cocaine use ($F(1,117)=5.21$, $p<.05$) were also significant (Fig. 2b). Simple effect analysis revealed that cocaine users did not differ from non-users in the no ADHD group ($F(1,117)=0.20$, $p=.66$), whereas cocaine use was associated with a significantly worse performance in the ADHD group ($F(1,117)=7.23$, $p<.01$).

Finally, a significant ADHD*cocaine use interaction effect ($F(1,117)=4.84$, $p<.05$) (Supplementary Fig. S3), as well as a main effect for cocaine on overmentalizing errors ($F(1,117)=8.57$, $p<.01$) appeared. The tendency to overmentalize was higher in cocaine users compared to non-users among the participants with ADHD ($F(1,117)=10.86$, $p<.001$).

3.4 Depressive Symptoms

The ANCOVA (with YoE and age as covariates) for the BDI score showed a significant main effect for group ($F(3,117)=13.82$, $p<.001$) as well a significant linear trend (controls<ADHD<CU-ADHD<CU+ADHD) ($p<.001$) (Fig. 3). CU+ADHD showed increased BDI scores versus all three other groups ($p<.001$). The two-way ANCOVA revealed significant main effects for ADHD ($F(3,117)=17.33$, $p<.001$) and cocaine use ($F(1,117)=24.24$, $p<.001$) and a significant interaction effect ($F(1,117)=4.06$, $p<.05$) (Fig. 2c), indicating an amplification of emotional disturbances in the

CU+ADHD group compared with the other three groups. Simple effect analyses showed that cocaine use is associated with significantly higher BDI scores in individuals with ($F(1,117)=18.47$, $p<.001$) and without ADHD ($F(1,117)=7.58$, $p<.01$).

4. DISCUSSION

The aim of the study was to investigate the interaction between ADHD and cocaine use with regard to non-social and social cognition and depressive symptoms. Detailed psychiatric diagnostics and hair toxicology were used to minimize the influence of psychiatric comorbidities and polytoxic drug use. We were able to demonstrate that cocaine users with ADHD symptoms (CU+ADHD) show stronger cognitive impairments than cocaine users without ADHD (CU-ADHD) or ADHD patients without cocaine use. Considering the increase in effect size, our data suggest that the combined detrimental effects of ADHD and cocaine on cognition are largely additive and that the factors seem to potentiate each other regarding depressive symptoms and mentalizing deficits. Thus, we supported our previous assumption that ADHD and cocaine use might exert mutually aggravating effects on cognitive performance and mental perspective-taking (Preller et al., 2014; Vonmoos et al., 2013a). Finally, adult ADHD patients without illicit drug consumption do not display impairments regarding cognitive and emotional empathy or mental and emotional perspective-taking.

Our study supports the hypothesis that the interaction of ADHD and cocaine use has a summative effect on general cognitive performance. Furthermore, we found only small to moderate performance deficits across all cognitive domains (d=0.17–0.37) in our sample of cocaine-naïve adults with ADHD. However, in addition to the limited power, rather small effect sizes can be expected in the executive functions of adult ADHD patients because of improved compensation for possible deficits with age (Nigg et al., 2005). Most studies reporting executive function deficits in adult ADHD patients have not assessed comorbidities, which may account for many findings of executive impairments (Nigg et al., 2005). Furthermore, previous findings suggest that declarative memory deficits are common in adult ADHD (Verster et al., 2010), which is in line with the present results: Our ADHD patients showed the strongest, although still not significant, impairment in this domain. Surprisingly, we did not find strong impairments in the attention domain, as might be expected in a disorder defined by attentional deficits. However, the distinction between adult ADHD patients and controls is usually based on omission errors and variability in reaction times in sustained attention and selective tasks over a minimum of 14 minutes (Conners and Sitarenios, 2011; Hervey et al., 2004). By contrast, our attention domain

included two parameters of a sustained attention task of a maximum length of 5 minutes and a supraspan parameter of a verbal learning task, which required less than 2 minutes. Furthermore, most of our cocaine-naive ADHD patients received pharmacological treatment with prescription stimulants prior to the study, which might have led to an underestimation of their potential cognitive deficits. However, acute cognitive improvements in adult ADHD patients medicated with methylphenidate should be expected primarily in the attention domain—less so in other cognitive domains (Advokat, 2010). On the other hand, because we asked our ADHD patients to abstain from their daily stimulant medication for at least 24h so as to exclude acute drug effects, the beneficial effects of methylphenidate are expected to no longer be present at the time of testing. Moreover, it should be noticed that our ADHD patients but also our cocaine using groups had a high level of functioning as all of the ADHD patients as well as 80% of the cocaine users were employed.

We have previously shown that dependent and recreational cocaine users display impaired explicit and implicit emotional empathy (Preller et al., 2014). Probably owing to the smaller sample sizes of the present cocaine groups and the mixture of recreational and dependent cocaine users, the present study showed only moderate effect sizes (d=0.24-0.55), which were, however, in the same range as reported in our previous publication (Preller et al., 2014). Furthermore, we previously demonstrated that CU+ADHD but not CU-ADHD individuals show significant mental perspective-taking deficits (as measured by MASC) (Preller et al., 2014), which is in line with the present results coming from an overlapping sample. Accordingly, the two-way ANCOVA of the MASC sum score revealed that the observed drop in performance in CU+ADHD can be explained by the mutual interaction of cocaine use and ADHD. Interestingly, it is not a general lack of Theory-of-Mind that accounts for group differences but rather the tendency of CU+ADHD to overmentalize. Thus, CU+ADHD might fail to understand the perspective of others because they overinterpret social signs (Preller et al., 2014).

The literature on social cognition in adult ADHD is surprisingly sparse and even in children with ADHD, empathy and Theory-of-Mind have rarely been investigated (Uekermann et al., 2010). However, there is some evidence that empathy and Theory-of-Mind may be affected in children with

ADHD (Braaten and Rosen, 2000; Buitelaar et al., 1999; Dyck et al., 2001). Because social cognition is essential for successful social interactions, the adult patients in our sample have perhaps developed strategies to compensate for possible social cognitive deficits. This may explain the lack of performance differences in social cognition in comparison to controls.

Regarding depressive symptoms, CU+ADHD displayed higher BDI scores than the controls, the ADHD patients, and CU-ADHD, indicating increased emotional burdens in CU+ADHD. Furthermore, a significant interaction effect indicated that cocaine use and ADHD mutually potentiate depressive symptoms. This finding is in line with the frequent comorbidity between depression and ADHD, as well as between depression and substance use disorders (Abraham and Fava, 1999; Daviss, 2008; Swendsen and Merikangas, 2000). Moreover, there is evidence for a relationship between depression and trait impulsivity (Swann et al., 2008), a core feature of ADHD (Wilson, 2007) that is also elevated in cocaine users (Vonmoos et al., 2013b).

As mentioned in the Introduction, there are potential commonalities between ADHD and cocaine use at the level of their neurobiological basis. The majority of imaging studies describes increased dopamine transporter density; decreased dopamine D_2 receptor availability; and decreased dopamine synthesis, storage, and release in both ADHD patients and chronic cocaine users (Trifilieff and Martinez, 2013; Zimmer, 2009). However, some conflicting results have been found regarding dopamine transporter density and the availability of D_2 receptors in ADHD patients (Volkow et al., 2009b), whereas for chronic cocaine users, the results seem to be more consistent. Additionally, recent data from our lab suggest that cognitive impairments in cocaine users are likely drug-induced (Vonmoos et al., 2014), whereas cognitive dysfunctions in ADHD should be inherent clinical features of the syndrome (Biederman, 2005). We therefore propose that cocaine-induced neurochemical adaptations amplify the ADHD-related abnormalities of the monoamine neurotransmitter systems (Tripp and Wickens, 2009). Although cocaine seems to deteriorate further the cognitive abilities of ADHD patients, the stimulant methylphenidate, which is used to target the cognitive problems of ADHD patients, has not been shown to lead to such an interaction (yet). This might be explained by

the different pharmacokinetics of these two substances. The strong cocaine-induced peaks of neurotransmitter release (Nestler, 2005) and the fast clearance of the drug seem to be more problematic with regard to neurochemical changes and associated cognitive dysfunctions than the slower brain uptake and clearance for (orally consumed) methylphenidate (Volkow et al., 1995; Volkow et al., 1998).

The current study has some limitations. Recent findings suggest that a single factor may account for interindividual variance in general psychopathology (e.g., Caspi's p-factor) (Caspi et al., 2014). Thus, the members of the CU+ADHD group might be more fraught in terms of general psychopathology than the CU-ADHD or ADHD patients. Because it is impossible to rule out this possibility in a study with a cross-sectional design, longitudinal investigations are needed on the interaction of cocaine use and ADHD. Furthermore, most of the ADHD patients in this study were previously medicated with prescription stimulants, whereas the CU+ADHD individuals were not (see above). However, at the test session they were abstinent for at least 24h. Thus, further investigations on the interaction of ADHD and cocaine should focus on unmedicated ADHD patients. Finally, the CU+ADHD displayed a more severe pattern of substance use specifically with regard to cannabis. Thus, it is not fully clear how cannabis use interacts with cocaine and ADHD on cognition. However, all relevant effect sizes remained the same if weekly cannabis use was introduced as a further covariate.

In conclusion, our data indicate that cognitive and social deficits are considerably worse in cocaine users with ADHD in comparison to cocaine users without ADHD and to ADHD patients without cocaine use. The cognitive impairments of ADHD and cocaine use seem to be additive, whereas cocaine use and adult ADHD appear to mutually amplify emotional disturbances and perspective-taking deficits in cocaine users with ADHD. Given the considerable comorbidity between ADHD and cocaine use disorder (Katusic et al., 2005; Wilens, 2007), longitudinal studies are needed to investigate the causal relationship behind the interaction of cocaine use and ADHD. Additionally, the impact of substances such as tobacco, alcohol and cannabis on cognitive and socio-cognitive deficits as well as on depressive symptoms need further investigation specifically in individuals with ADHD and cocaine

use. Finally, the present data strongly suggest that ADHD patients should be better informed about their specific cognitive and emotional risks of cocaine abuse.

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Table 1: Demographic data and drug use (means and standard deviations)

	Controls	ADHD	CU-ADHD	CU+ADHD	F	χ^2	*t* test	df, df_{err}	*p*
n (%)	40 (32.5)	29 (23.5)	30 (24.5)	24 (19.5)					
Age, years	26.1 (5.5)	25.7 (6.3)	26.9 (6)	27.7 (6.6)	0.59			3, 119	.625
Sex (female/male)	22/18	17/12	13/17	6/18		7.42		3	.060
Years of education	11.5 (1.6)	11.7 (1.8)	11 (1.9)	10.2 (1.4)*††	4.49			3, 119	**.005**
Verbal intelligence	104.3 (8.1)	104.6 (9.7)	101.6 (10)	97.8 (7.7)*†	3.39			3, 119	**.020**
ADHD-SR	7.5 (5.3)	29.2 (10.9)***	11.1 (7.3)†††	25.7 (8.2)***‡‡‡	57.05			3, 119	**.000**
Craving for Cocaine (0-70)	-	-	18.3 (8.5)	23.3 (12.9)			-1.74	52	.088
Tobacco									
Smoking status (y/n)[a]	22/18	11/18	19/11	19/5		9.69		3	**.021**
Dependence (y/n)[b]	9/31	3/26	15/15	10/14		13.66		3	**.003**
Cigarettes per day	5.3 (7.5)	2.7 (5.7)	11 (12.1)††	13 (10.2)**††††	7.87			3, 119	**.000**
Years of use	5.3 (5.5)	4.7 (7.4)	7.7 (7)	10.6 (6.1)*††	4.71			3, 119	**.004**
Alcohol									
Alcohol use (y/n)[a]	39/1	29/0	30/0	24/0		2.09			.554
Dependence (y/n)[c]	0/40	1/28	4/26	2/22		6.26		3	.100
Grams per week[a]	110.6 (147.2)	53.1 (40.2)	194.4 (238.5)††	177.2 (146.7)†	4.77			3, 119	**.004**
Years of use	7.9 (4.4)	7.7 (6.7)	9.6 (5.1)	10.6 (5.4)†	1.91			3, 119	.131
Cocaine									
Dependence (y/n)[c]	-	-	6/24	7/14		0.61		1	.528
Grams per week[a]	-	-	2.3 (3.1)	2.1 (3.1)			0.27	52	.789
Years of use	-	-	6.3 (5.1)	7 (4.9)			-0.53	52	.599
Last consumption (days)	-	-	22.3 (33) n=30	26.6 (35.1) n=24			-.47	52	.643
Cumulative dose (grams)	-	-	1932.6 (5169.8)	3174.2 (8456)			-0.67	52	.509
Positive urine test[d](%)	0 (0)	0 (0)	8 (27.6)	5 (20.8)		.32		1	.570
Hair analysis pg/mg[e]	0 (0)	0 (0)	5212.8 (9195.6)	5509.8 (9517.2)	7.47			3, 118	**.000**
Methylphenidate									
Tablets per week[a,f]	0 (0)	15.9 (18.4)	0.9 (2.9)†††	1.9 (4)†††	20.17			3, 119	**.000**
Years of use	0 (0)	2.6 (3.7)	0.1 (0.3)†††	0.1 (0.2)†††	15.44			3, 119	**.000**
Last consumption (days)		8.8 (19.4) n=24	48.3 (53.7) n=5				-2.94	27	**.007**
Cumulative dose[f]	0 (0)	2001 (2672)	36.8 (124.9)†††	49.3 (133.3)†††	17.12			3, 119	**.000**

Urine toxicology MPH ng/ml	na	1.14 (3.4) n=27	na	na				
Urine tox. Ritalin acid ng/ml	na	327.94 (721.8) n=27	na	na				
Hair analysis pg/mg[e]	0 (0)	191 (342.4)	15.8 (77.8)	0 (0)	8.84		3	**.000**
Cannabis								
Grams per week[a]	0.2 (0.6)	0.1 (0.4)	0.2 (0.3)	2.2 (4.3)***†††‡‡‡	7.45		3, 119	**.000**
Years of use	3.5 (4.2)	2.7 (4.3)	6.6 (5.1)†	8.2 (6.5)**†††	7.69		3, 119	**.000**
Cumulative dose (grams)	919.8 (4372.6)	235.2 (613.7)	972.3 (1658.2)	1989.3 (3303.2)	1.49		3, 119	.222
Last consumption (days)	35 (43.4) n=17	27.8 (29.7) n=8	25.2 (29.3) n=22	18 (28.3) n=18	0.77		3, 61	.514
Positive urine testing[d] (%)	3 (7.5)	3 (10.3)	3 (10.3)	10 (41.7)	15.62		3	**.001**

Significant *p*-values are shown in bold. Statistical tests: ANOVA (all groups), $\chi 2$ test (all groups or cocaine user groups) for frequency data or independent t test (two groups).
ADHD, attention-deficit/hyperactivity disorder; ADHD-SR, ADHD self-rating scale; CU+ADHD, cocaine users with ADHD; CU-ADHD, cocaine users without ADHD; MPH, methylphenidate.
Consumption per week, duration of use, and cumulative dose are averages within the total group.
Last consumption is an average only for persons who used the drug within the past 6 months. In this case, sample size (n) is shown.
[a] During the past 6 months.
[b] Fagerström Test > 2 points.
[c] According to DSM-IV criteria.
[d] For cut-offs, see the Supplementary Methods S2. One urine sample (CU-ADHD) was missing.
[e] One hair sample (ADHD) is missing.
[f] In 10-mg tablets.
Sidak post-hoc tests vs. controls: **p*<.05, ** *p* <.01; vs. ADHD † *p* <.05, †† *p* <.01, ††† *p* <.001; vs. CU-ADHD: ‡‡‡ *p* <.001

Figure Captions

Figure 1: Mean z-scores and standard errors for the four cognitive domains and the global cognitive index

Values corrected for years of education and age. Sidak post-hoc tests vs. controls: **p<.01, ***p<.001; vs. ADHD: ††p<.01, †††p<.001; vs. CU-: ‡p<.05. Cohen's d effect sizes for group comparisons vs. controls are shown.

Figure 2: Mean scores and standard errors for a) the global cognitive index (GCI), b) Theory-of-Mind, and c) the Beck Depression Inventory (BDI) for all participants (n=123)

Two-way analysis of covariance (ANCOVA) revealed summative effects of ADHD and cocaine use on cognition (p>.05). However, these two factors show a significant interaction effect on Theory-of-Mind and depressive symptoms (both p<.05), indicating a mutual reinforcement. ADHD = attention-deficit/hyperactivity disorder, MASC = Movie for the Assessment of Social Cognition.

Figure 3: Mean sum score and standard errors for the Beck Depression Inventory

Values corrected for years of education and age. Sidak post-hoc tests vs. controls: ***p<.001; vs. ADHD: †††p<.001; vs. CU: ‡‡‡p<.001. Cohen's d effect sizes for group comparisons vs. controls are also shown.

Fig. 1

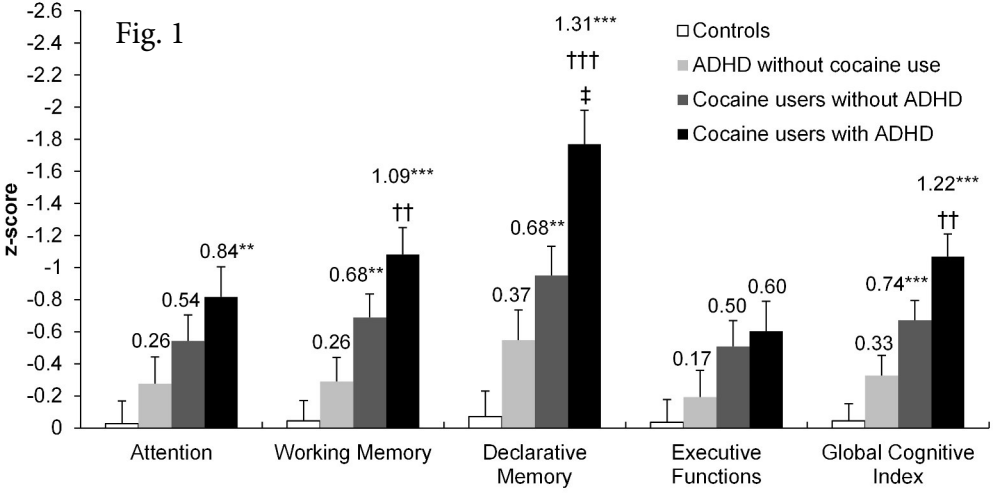
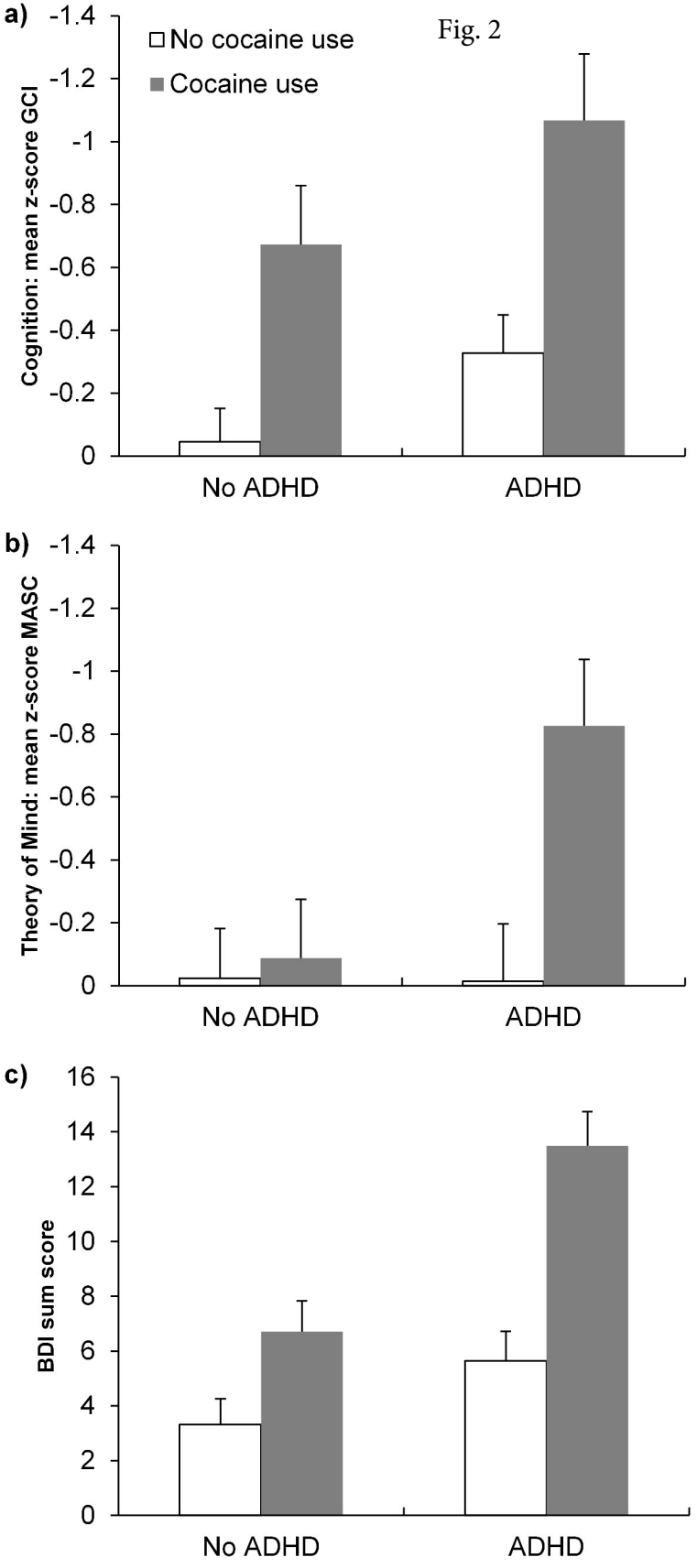

z-score
-2.6
-2.4
-2.2
-2
-1.8
-1.6
-1.4
-1.2
-1
-0.8
-0.6
-0.4
-0.2
0
Controls
ADHD without cocaine use
Cocaine users without ADHD
Cocaine users with ADHD
0.26
0.54
0.84**
0.26
0.68**
1.09***
††
0.37
0.68**
1.31***
†††
‡
0.17
0.50
0.60
0.33
0.74***
1.22***
††
Attention
Working Memory
Declarative Memory
Executive Functions
Global Cognitive Index

Fig. 2


a)
No cocaine use
Cocaine use
Cognition: mean z-score GCI
-1.4
-1.2
-1
-0.8
-0.6
-0.4
-0.2
0
No ADHD
ADHD
b)
Theory of Mind: mean z-score MASC
-1.4
-1.2
-1
-0.8
-0.6
-0.4
-0.2
0
No ADHD
ADHD
c)
BDI sum score
16
14
12
10
8
6
4
2
0
No ADHD
ADHD

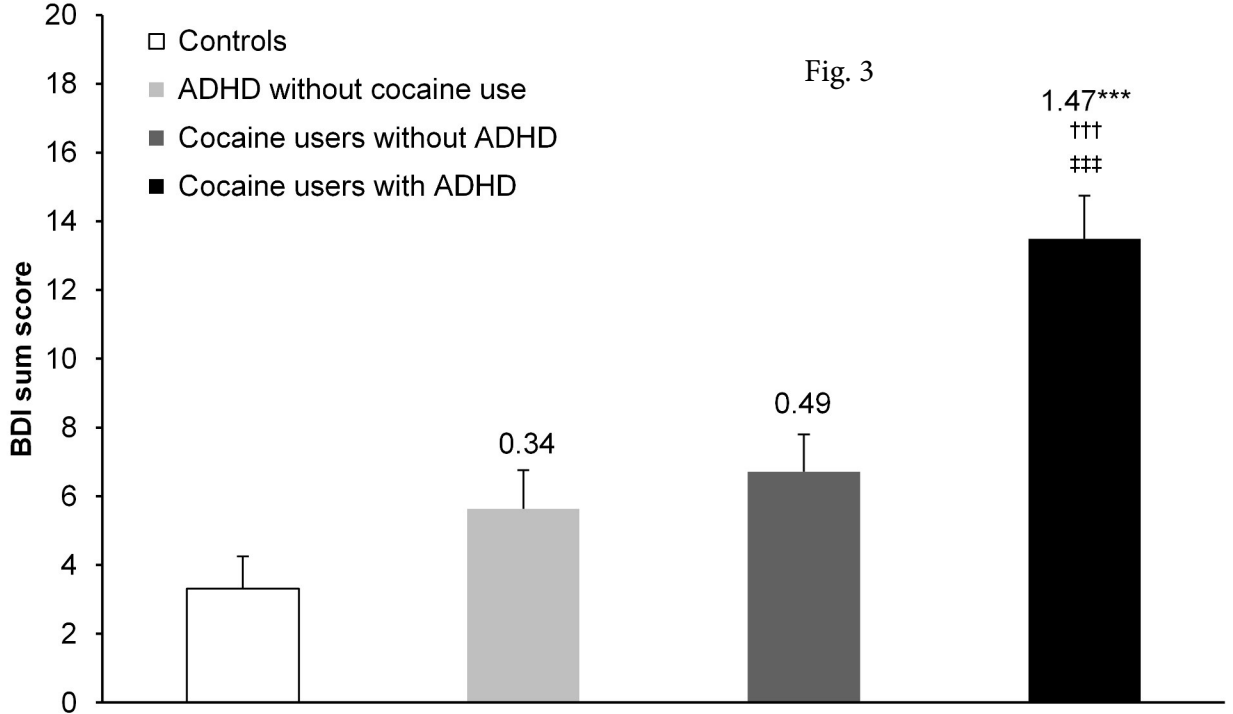

Controls
ADHD without cocaine use
Cocaine users without ADHD
Cocaine users with ADHD
BDI sum score
20
18
16
14
12
10
8
6
4
2
0
0.34
0.49
1.47***
†††
‡‡‡

Fig. 3

Data Supplement

Article Title: Cognitive and emotional impairments in adults with attention-deficit/hyperactivity disorder and cocaine use

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List of supplementary material for the article

Methods S1: Recruitment and selection

Out of the already existing pool of participants from the *Zurich Cocaine Cognition Study (ZuCo²St)* (Preller et al., 2014; Vonmoos et al., 2014), 24 cocaine users with ADHD (CU+ADHD), 30 cocaine users without ADHD (CU-ADHD), and 22 stimulant-naïve healthy controls were identified for the present analyses. Eighteen stimulant-naïve healthy controls and 29 ADHD patients without cocaine use were additionally recruited resulting in a total sample of 123 participants consisting of 40 stimulant-naïve healthy controls, 24 CU+ADHD, 30 CU-ADHD, and 29 ADHD patients without cocaine use matched for age and sex. ADHD patients were recruited from the ADHD special outpatient clinic of the Department of Psychiatry, Psychotherapy, and Psychosomatics at the Psychiatric Hospital of the University of Zurich. Some patients as well as controls were also recruited by advertisements in various online media and flyers distributed in various buildings of the University of Zurich. Candidates underwent a brief telephone screening to assess their study eligibility. All subjects were aged between 18 and 60 years and had sufficient German language skills. In total, 32 ADHD patients were tested whereof 3 ADHD patients had to be excluded because positive hair analyses revealed undeclared drug use contradicting the inclusion criteria (cocaine use or excessive MDMA use).

Methods S2: Urine and hair toxicology

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany). For the detection of illegal drug use, the following cut-offs have been applied (Bush, 2008): Cannabis, 50 ng/ml; cocaine, 150 ng/ml; and amphetamines, 500 ng/ml.

To objectively characterize drug use over the last six months, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16 hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven,

Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively. According to the Society of Hair Testing (Society of Hair, 2004), the following cut-offs have been applied: cocaine, 500 pg/mg; amphetamine, 200 pg/mg; and MDMA, 200 pg/mg.

Methods S3: Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group as published before (Vonmoos et al., 2013). If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains attention, working memory, declarative memory, and executive function. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention: To assess attentional capacity, we focused primarily on sustained attention by including the two Rapid Visual Information Processing (RVP) parameters discrimination performance A' and total of hits (Jones et al., 1992). In order to diversify this domain we added the Ray Auditory Verbal Learning Test (RAVLT) parameter trial 1, a supraspan measure with a large attentional component (Lezak et al., 2004).

Working Memory: The Spatial Working Memory (SWM) parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory (Morris et al., 1988). The Letter Number Sequencing Test (LNST) measured the verbal working memory by summing up the number of correct responses (Wechsler, 1997). The third parameter was the number of correctly located patterns after the first presentation, a Paired Associates Learning (PAL) parameter measuring primarily a visual working memory component (Sahakian et al., 1988).

Declarative memory: The RAVLT was administered to assess the verbal declarative memory performance (Helmstaedter et al., 2001). Performance was measured by the parameters learning performance (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (p(A)) (Helmstaedter et al., 2001). To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials (Sahakian et al., 1988).

Executive Functions: The Intra/Extra-Dimensional Set Shifting (IED) assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility (Downes et al., 1989). The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies (Morris et al., 1988), and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions(Alexander et al., 2003; Benedict et al., 2005; Jokeit et al., 1997) and related with measures of executive functions (Beebe et al., 2000).

Methods S4: Social cognition tasks

In brief, the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006) consists of a movie pausing 45 times and participants are asked about the actors' feelings, thoughts, and intentions during the presented social situation in a multiple-choice format. Besides the correct answer, three wrong answers are presented, each reflecting a different error type: insufficient mental state interference (undermentalizing), excessive (overmentalizing) and non-mental state interferences (physical causation, no *Theory-of-Mind*). We analyzed these three error types separately (see Supplementary material, eFigure 1) as well as the MASC sum score reflecting the total number of correct answers. These four variables were z-transformed on the basis of means and standard deviations of the control group.

The PC-assisted Multifaceted Empathy Test (MET) (Dziobek et al., 2008) contains photographs of everyday-life situations allowing for interpretation of the emotional mental states of the depicted person based on her/his facial expression and posture. By ratings on a visual analogue scale, explicit emotional empathy (EEE) is assessed ("How concerned are you for this person?"). Likewise, implicit emotional empathy (IEE) is measured by arousal ratings ("How calm/aroused does this picture make you feel?"). Cognitive empathy (CE) is measured by asking the participants to choose one out of four words to describe the person's feeling. These three empathy parameters were also z-transformed on the basis of means and standard deviations of the control group.

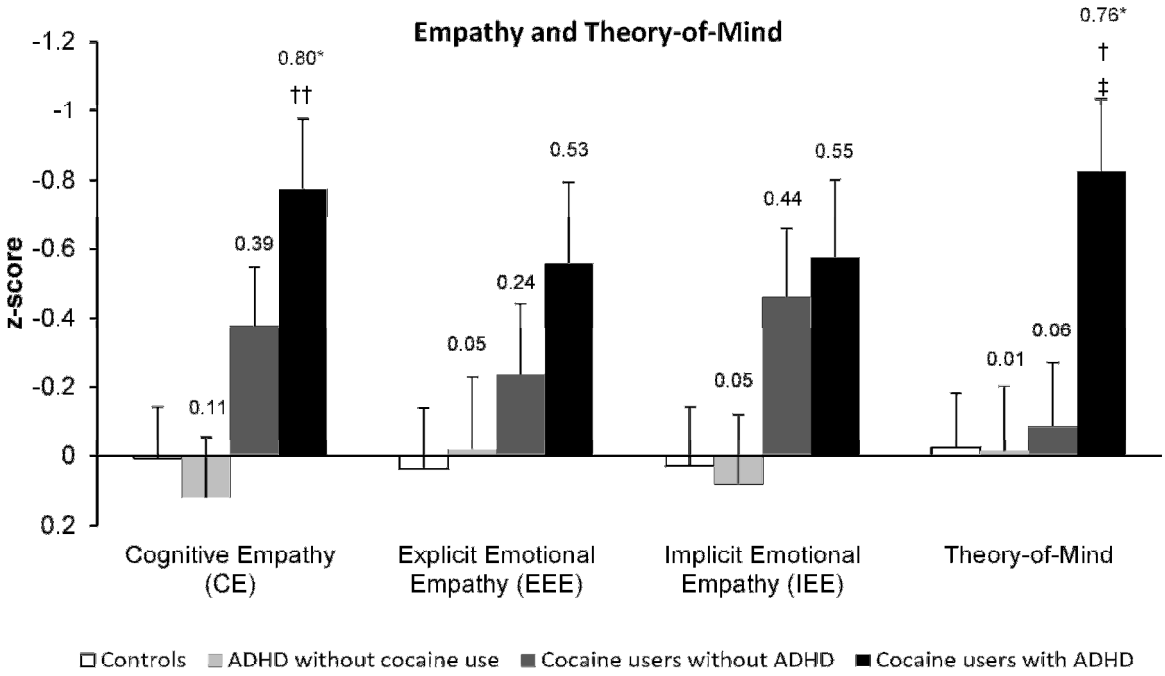

Figure S1: Group comparisons for cognitive empathy, explicit and implicit emotional empathies, and Theory of Mind. Mean z-scores and standard errors are shown. Values corrected for years of education and age. Sidak post-hoc tests vs. controls: *p<.05; vs. ADHD: †p<.05, ††p<.01; vs. CU-ADHD: ‡p<.05. Cohen's d effect sizes for group comparisons vs. controls are shown.

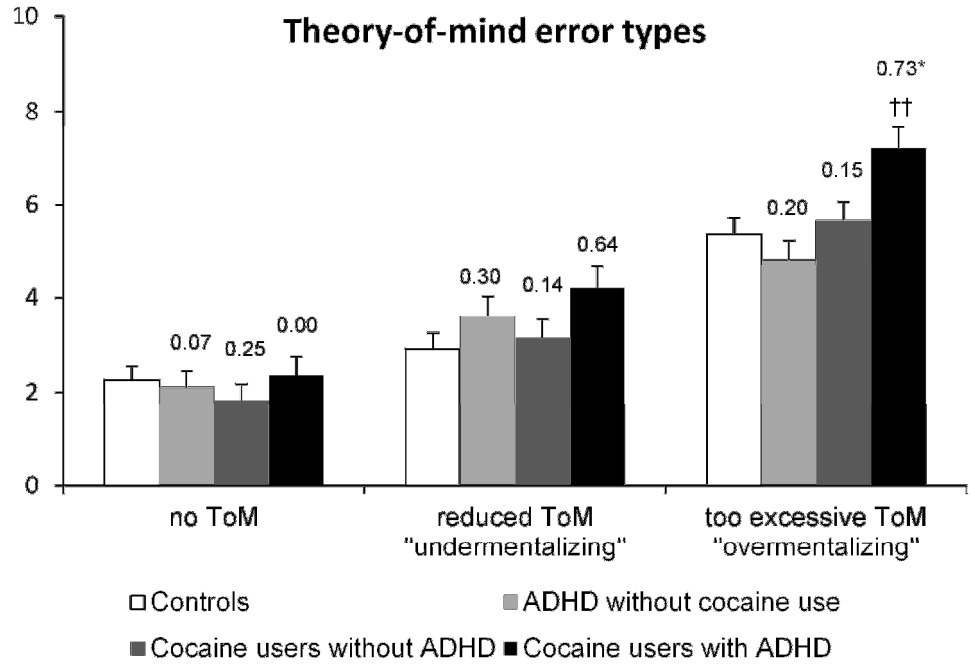

Figure S2: Group comparisons of the three error types for the assessment of social cognition. Mean of error types and standard errors for the assessment of social cognition (MASC) for cocaine users with (n=24) and without (n=30) ADHD, ADHD patients (n=29), and healthy controls (n=40). Cohen's d effect sizes for group comparisons vs. the control group are shown. ANCOVA (with years of education and age as covariates) for overmentalizing (too excessive) yielded a main effect for group [$F(3,117)=4.08$, $p<.01$] Sidak post-hoc tests revealed that cocaine users with ADHD made more errors than controls (*$p<.05$) and ADHD patients (††$p<.01$, $d=0.93$) in overmentalizig.

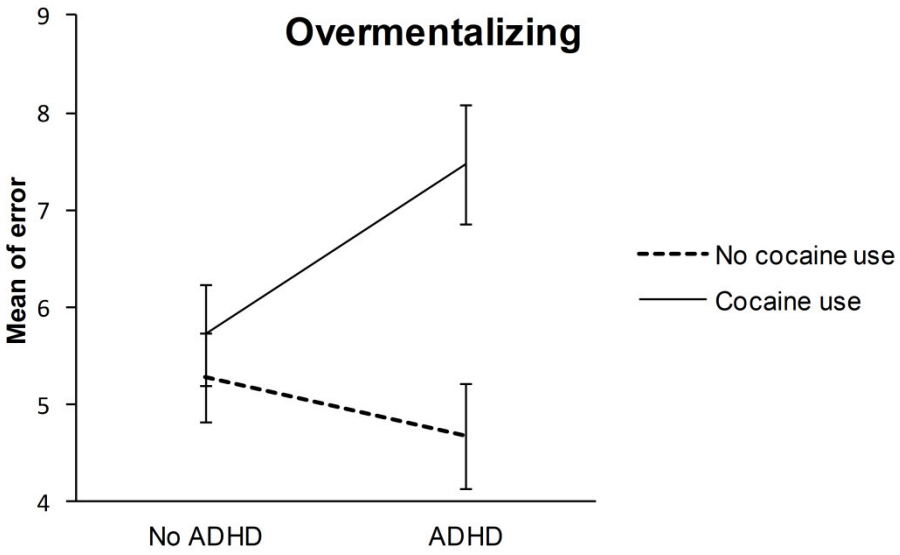

Figure S3: Interaction graph for overmentalizing. Mean overmentalizing error scores and standard errors for the assessment of social cognition (MASC) over all participants (n=123). Two-way ANCOVA (with years of education and age as covariates) with the fixed factors ADHD and CU revealed a significant interaction [$F(1,117) = 4.84$, $p<.05$] and a significant main effect for cocaine use ($p<.01$).

Table S1: Global cognitive index (GCI), the four cognitive domain z-scores, and neuropsychological test scores.

	Controls	ADHD	CU-ADHD	CU+ADHD	F	*df*	*p*
Global Cognitive Index (GCI)	-0.05 (0.11)	-0.33 (0.13)	-0.67 (0.12)**	-1.07 (0.14)***††	12.115	3	.000
Neurocognitive domain scores							
Attention	-0.03 (0.14)	-0.28 (0.17)	-0.54 (0.16)	-0.82 (0.19)**	4.159	3	.008
Working memory	-0.05 (0.13)	-0.29 (0.15)	-0.69 (0.15)**	-1.08 (0.17)***†††	8.871	3	.000
Declarative memory	-0.07 (0.16)	-0.55 (0.19)	-0.95 (0.18)**	-1.77 (0.21)***††††‡	14.070	3	.000
Executive functions	-0.04 (0.14)	-0.19 (0.17)	-0.51 (0.16)	-0.6 (0.19)	2.682	3	.050
Neuropsychological test scores							
Attention							
RVP Discrimination performance A'	0.92 (0.01)	0.91 (0.01)	0.9 (0.01)	0.89 (0.01)	2.090	3	.105
RVP Total hits	18.64 (0.78)	17.51 (0.93)	16.78 (0.9)	15.44 (1.1)	1.973	3	.122
RAVLT Supraspan trial 1	9.97 (0.33)	9.47 (0.39)	8.62 (0.37)*	7.99 (0.46)**	4.922	3	.003
Working memory							
LNST Score	16.49 (0.47)	15.89 (0.56)	14.51 (0.54)*	13.2 (0.66)***†	6.246	3	.001
SWM Total errors	17.35 (2.43)	16.59 (2.88)	26.74 (2.79)	26.55 (3.4)	3.602	3	.016
PAL First trial memory score	16.67 (0.5)	14.95 (0.59)	15.11 (0.57)	13.15 (0.7)***	5.783	3	.001
Declarative memory							
RAVLT Learning performance (∑ trials 1-5)	65.59 (1.12)	63.08 (1.32)	59.56 (1.28)**	55.42 (1.56)***††	10.138	3	.000
RAVLT Adjusted recognition performance p(A)	0.94 (0.02)	0.91 (0.02)	0.84 (0.02)***	0.83 (0.02)***†	9.045	3	.000
RAVLT Delayed recall trial 7	13.92 (0.32)	13.43 (0.38)	12.73 (0.37)	11.09 (0.45)***†††‡	8.965	3	.000
PAL Total errors adjusted	7.06 (1.43)	11.1 (1.7)	9.1 (1.64)	18.12 (2.03)***‡‡	6.943	3	.000
PAL Total trials adjusted	7.67 (0.36)	8.34 (0.43)	8.11 (0.42)	10.36 (0.51)**†‡‡	6.402	3	.000
Executive functions							
IED Total errors adjusted	26.54 (5.4)	30.56 (6.41)	32.7 (6.21)	23.56 (7.57)	.378	3	.769
IED Total trials adjusted	97.98 (9.71)	106.15 (11.52)	108.97 (11.16)	95.16 (13.6)	.319	3	.812
SWM Strategy score	31.58 (0.86)	30.39 (1.02)	33.22 (0.99)	33.22 (1.2)	1.679	3	.175
RAVLT Recall consistency in %	94.45 (1.36)	91.93 (1.61)	89.04 (1.56)	83.74 (1.91)***†	7.148	3	.000

Data are estimated means and standard errors for controls (n=40), ADHD patients (29), CU-ADHD (30), and CU+ADHD (24). Statistical Test: ANCOVA over all groups with age and years of education as covariates. In PAL and SWM one subject is missing due to a technical failure. RVP=Rapid Visual Information Processing. RAVLT=Rey Auditory Verbal Learning Test. LNST=Letter Number Sequencing Task. SWM=Spatial Working Memory. PAL=Paired Associates Learning. IED=Intra-Extra Dimensional Set Shift.

Sidak post-hoc tests: vs. controls: * p <.05, ** p <.01, *** p <.001, vs. ADHD † p <.05, †† p <.01, ††† p <.001, vs. CU-ADHD: ‡ p <.05 ‡‡ p <.01.

Table S2: Correlations between craving for cocaine and outcome measures

	CCQ sum score
Attention	-0.184
Working memory	-0.182
Declarative memory	-0.147
Executive functions	-0.177
Global cognitive Index	-0.212
MET[a]: explicit emotional empathy	-0.043
MET[a]: implicit emotional empathy	-0.019
MET[a]: cognitive empathy	-0.21
MASC[b]: Theory-of-Mind	-0.299
BDI[c] sum score	0.216
ADHD-SR sum score[d]	0.251

Correlations between the CCQ sum score and measures of cognitive performance as well as depressive symptoms and ADHD scores in cocaine users (n=54) are shown. No significant correlations ($p<.01$) were found.

[a] Multifaceted Empathy Test

[b] Movie for the Assessment of social Cognition

[c] Beck's Depression Inventory

[d] ADHD self-rating Scale; Sum of the Items 1 to 18.

Table S3: Drug use patterns.

	Controls	ADHD	CU-ADHD	CU+ADHD	X^2 / F / *t*	*df*, df_{err}	*p*
Amphetamine							
Grams per week[a]	0 (0)	0 (0)	0 (0.1)	0.1 (0.3)*	3.338	3, 119	**.022**
Years of use	0 (0)	0.2 (0.7)	0.8 (2.1)	2.9 (3.8)***†††‡‡	12.277	3, 119	**.000**
Cumulative dose (grams)	0 (0)	0.1 (0.4)	8.2 (22.4)	48.1 (88.9)***†††‡‡	8.386	3, 119	**.000**
Last consumption (days)	0 (0)	60.8 n=1	59.9 (49.2) n=8	82.1 (51.7) n=10	0.454	2, 16	.643
Positive urine testing[b]	0 (0%)	2 (6.9%)	1 (3.4%)	1 (4.2%)	2.615	3	.455
Hair analysis pg/mg	0 (0)	27.3 (140.7)	24.3 (83.3)	65.4 (171.4)	1.794	3, 118	.152
MDMA							
Tablets per week[a,c]	0 (0)	0 (0.1)	0.1 (0.3)	0.4 (2)	1.339	3, 119	.265
Years of use	0 (0)	0.4 (1.2)	2.1 (3.4)*	3.7 (5.5)***†††	9.137	3, 119	**.000**
Cumulative dose (tablets)	0.1 (0.4)	6.8 (22.9)	37.9 (70.6)	108.3 (383.1)	2.242	3, 119	.087
Last consumption (days)	0 (0)	91.2 n=1	56.4 (44.3) n=9	66.4 (31.3) n=9	0.440	2, 16	.652
Hair analysis pg/mg	0 (0)	0.9 (4.7)	406.3 (1219.8)	387.3 (967.9)	2.894	3, 118	**.038**

Significant p-values are shown in bold. Statistical tests: ANOVA (all groups) and t-tests (two groups).
Consumption per week, duration of use, and cumulative dose are averaged within the total group.
Last consumption is averaged only for persons who used the drug within the past 6 months. In this case, sample size (n) is shown.
[a]Averaged for the past six month.
[b]For cut-offs see online Methods S2, one urine sample (CU-ADHD) is missing.
[c]In tablets à 100 mg.
Sidak post-hoc tests: vs. controls: *<.05, **<.01, ***<.001, vs. ADHD †<.05, †††<.001, vs. CU-ADHD: ‡‡‡<.001

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